REMARKS/ARGUMENTS

Applicants would like to thank the Examiner for the courtesy of the telephone interview conducted on November 6, 2003. At the interview, Applicants' representatives discussed the prior art of record (Nycz *et al.*, *Analytical Biochemistry*, 1998, 259:226-234; hereinafter "Nycz") and the Examiner agreed that Nycz does not teach synthesis of cDNAs longer than 600 nucleotides.

Applicants acknowledge with thanks that the amendment filed May 14, 2003 was entered.

I. Amendments to the Specification

The specification has been amended to correct a minor typographical error at page 7. It is submitted that no new matter has been added.

II. Amendments to the Claims

Claims 53-58 and 66-79 are pending in this application.

Claim 66 has been cancelled without prejudice or disclaimer of the subject matter contained therein. Applicants reserve the right to pursue the invention claimed therein in this or future related applications.

Claim 80, which is dependent on claim 53, has been newly added. Claim 80 incorporates some of the subject matter of cancelled claim 66 in addition to subject matter to which Applicants are entitled.

Claims 53, 58 and 67-79 have been currently amended.

The number of pending claims is unchanged with these amendments.

Support for the claim amendments and newly added claim 80 can be found throughout the application as filed. Specifically, support for the amendment to claim 53, and for the new dependent claim (claim 80) can be found at page 21, lines 13-18; page 22, lines 14-18; page 23, lines 14-22 continuing onto page 24, line 1; and page 25, lines 6-19. Dependent claims 66-79 have been amended to correct claim dependency and/or minor clerical errors. It is submitted that no new matter has been added.

As the amended claims present no new issue of patentability and put the claims in condition for allowance, entry of the claims is requested.

III. Rejections under 35 U.S.C. § 103(a)

(a) Claims 53-56, 58 and 66-79 stand rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Nycz.

The subject matter of the claimed invention is directed to a method for synthesizing cDNA by enhancing the processivity of a reverse transcriptase which comprises transcribing RNA with a reverse transcriptase in the presence of a single-strand binding protein under conditions to produce one or more cDNAs longer than about 600 nucleotides.

The Office Action acknowledges that Nycz does not disclose the completed reverse transcription of mRNA molecules, which are greater than 600 nucleotides in length. (Office Action, page 3, first full paragraph). The Office Action argues, however, that "one of ordinary skill in the art at the time of the instant invention would have been motivated to combine of [*sic*] reverse transcriptase and single stranded binding protein because with the inclusion of the single-strand binding protein, the amplification efficiency increases (See p.226, column 1, the Abstract)." (Office Action, page 3, second full paragraph). The Office Action further alleges that "one of ordinary skill would have also varied the reaction condition by optimizing the concentration of the single-strand binding protein and the temperature of the reaction in order to optimize the reaction condition to maximize the amount of transcription product as it was routine procedure to optimize reagent condition in assays." (Office Action, page 3, second full paragraph). Thus, the Office Action concludes that it would have been *prima facie* obvious to carry out the method as claimed. Applicants respectfully disagree and traverse the rejection.

To establish a *prima facie* case of obviousness, there must be some teaching, suggestion or motivation either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Nycz is directed to developing methods for quantitating viral loads in an accurate, simple and fast manner so that the clinical laboratory can provide timely quantitation results on clinical specimens (see, page 226, right column, first incomplete paragraph and last

paragraph). Nycz restricts itself to amplifying short regions of viral genes. Specifically, Nycz performs amplifications of regions that are at most 100 nucleotides in length (see Figure 4, page 230). This reference provides no motivation to provide cDNAs longer than about 100 nucleotides, and in fact, teaches away from Applicants' claimed invention, because, for example, increasing fragment size can increase the time to quantitate the viral load and can unduly complicate analysis when an accurate and simple assay is the goal.

The Office Action suggests that there is a motivation to modify the Nycz procedure because Nycz teaches an increase in amplification efficiency in the presence of a single strand binding protein. Nycz describes a quantitative reverse transcription strand displacement amplification (QRT-SDA) procedure that consists of two components: (1) target generation using a reverse transcriptase to produce cDNA, and (2) exponential amplification of the cDNA target by strand displacement replication (see, page 226, right column, first full paragraph). In describing the reaction, Nycz stated that amplification efficiency was improved "by including the single strand binding protein from gene 32 of T4 bacteriophage (T4gp32) ***to enhance strand displacement replication***" (Abstract, page 226). Thus, Nycz's statement regarding amplification efficiency indicates that single strand binding protein enhances the second step of QRT-SDA, namely, strand displacement replication. Nycz's assessment is consistent with the use of T4 gp32 in a T4 DNA replication step that is similar to SDA, and is also consistent with the use of T4gp32 in PCR reactions to amplify DNA[1].

In contrast and unexpectedly, Applicants have demonstrated that single strand binding protein actually enhances processivity of cDNA synthesis, the first step of Nycz's procedure. Figure 5 in the specification demonstrates that addition of single strand binding protein enhances the processivity of reverse transcriptase thereby enabling synthesis of long cDNAs. Figure 5 depicts the results of an agarose gel electrophoresis of cDNA products from reverse transcription reactions containing increasing amounts of T4gp32 single-strand binding protein. Increasing the amount of T4gp32 in the reverse transcription reaction of the RNA template reduces the inter-

[1] It should also be noted that Nycz provides no data to establish the basis for including single strand binding protein in any of its reactions. As such, in the absence of a comparison between a reaction containing and lacking a single strand binding protein, there is no scientific evidence in Nycz that the inclusion of single strand binding protein results in an improvement in amplification efficiency in either the reverse transcription or the amplification reactions.

band smear and secondary bands and permits the production of longer cDNAs. Bands of higher molecular weight and without inter-band smears indicate better processivity of the reverse transcriptase. Thus, these data show that inclusion of single strand binding protein significantly and unexpectedly increases the processivity of reverse transcription thus, producing full-length cDNAs.

The Office Action also suggested that Nycz discloses synthesizing cDNA from mRNA molecules that are greater than 600 nucleotides (Office Action, page 4, last paragraph). However, the size of a template is not solely determinative of the size of the cDNA produced, but rather the produced cDNA also depends on the number and placement of the primers on the template. In Nycz, the longest cDNA that could be synthesized is 201 nucleotides in length.

Hence, Nycz does not suggest addition of single strand binding protein to a reverse transcription process to enhance the processivity of the reverse transcriptase to produce cDNAs longer than 600 nucleotides. Moreover, even if Nycz did, *pro arguendo*, Applicants have demonstrated that single strand binding protein unexpectedly enhances reverse transcription reactions.

Accordingly the currently pending claims are not rendered obvious by Nycz. In view of the above comments, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

(b) Claim 57 stands rejected under 35 U.S.C. § 103(a) as purportedly rendered obvious by Nycz in view of Cleuziat *et al.* (U.S. Patent No. 5,849,547; hereinafter "Cleuziat").

As discussed above, Nycz provides no teaching or motivation to arrive at Applicants' invention. This deficiency is not remedied by Cleuziat.

Cleuziat describes a method of amplifying a target nucleic acid sequence (RNA and/or DNA) by a transcription reaction using strand displacement. It discloses the possibility of using reverse transcriptase to make cDNA and single strand binding protein from *E. coli* for strand displacement. However, this reference does not provide any motivation or teaching to combine reverse transcriptase and single strand binding protein to synthesize cDNAs longer than 600

nucleotides from RNA molecules. Furthermore, the Examiner has provided no basis in Cleuziat to combine it with Nycz.

Because Cleuziat fails to teach or suggest a method of synthesizing cDNA greater than 600 nucleotides, the combined references do not render the claimed invention obvious.

Therefore, it is respectfully requested that this rejection be withdrawn.

V. Conclusion

Applicants believe that all of the outstanding rejections of record have been overcome by amendment and/or argument. Accordingly, the claims are now believed to be in condition for allowance. Applicants respectfully request that the Examiner issue a timely Notice of Allowance.

Applicants enclose herewith a petition requesting a one-month extension of time, to respond to the Office Action. Please apply the fee for the one-month extension of time, pursuant to 37 C.F.R. § 1.17(a)(1), of $55.00 to our Deposit Account No. 08-0219. If any additional fees are due, please charge any payments due or credit any overpayments to our Deposit Account No. 08-0219.

The Examiner is invited to telephone the undersigned at the telephone number given below in order to expedite the prosecution of the instant application.

Respectfully submitted,

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